Bendamustine: New Data On An Old Drug

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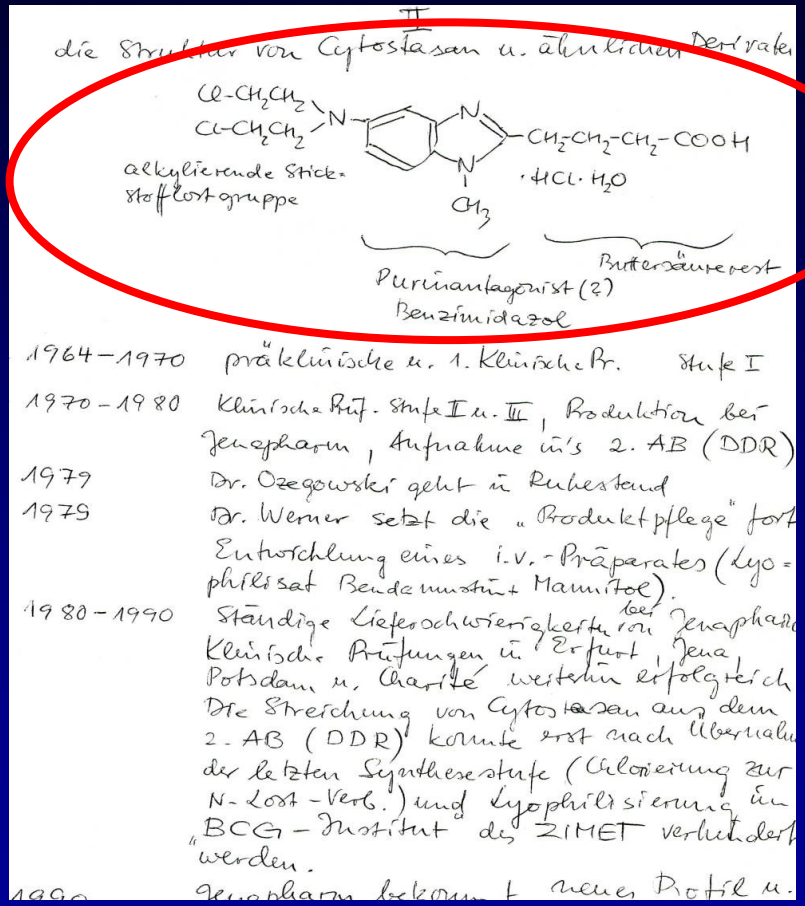
Conflicts

- Lecturing – Astellas
- Consulting – Abbvie, Acerta/Astra Zeneca, Bayer, Morphosys, Roche-Genentech, Gilead, TG Therapeutics
- Research support (to institution) – Abbvie, Acerta, TG Therapeutics, Roche-Genentech

Birth certificate of Bendamustine: 1962

„Parents“

Ozegowski & coworkers



Conceptual idea:

to improve cytostatic effectivity by combining alkylating and anti-metabolite properties in one substance

Bendamustine: Background

- Developed in the 1960s in East Germany as a “bifunctional” alkylating agent
- Non-cross resistant with other alkylating agents
- Induces more durable DNA damage than other alkylating agents, resulting in rapid cell death through apoptosis and mitotic catastrophe
- German studies showed single-agent activity in NHL, CLL, multiple myeloma, and breast cancer

Bendamustine in the US: Historical Perspective

- March 2000 - meeting with Ribosepharm (A. Pieper) at German Cancer Congress in Berlin
- October 2001 - Satellite Symposium to ECCO in Lisbon brought together East/West
- May 2002 - meeting between Ribosepharm and Salmedix
- Sept 29, 2003 - First patient entered onto a clinical trial with bendamustine in the US
- March 30, 2008 - Bendamustine approved by FDA for CLL
- October 31, 2008 – Approved for rituximab refractory F-NHL

Use of Bendamustine in Lymphomas

- Follicular lymphoma
- Mantle cell lymphoma
- CLL
- Other indolent NHL (WM, MZL, SLL)

- HL
- DLBCL
- T-NHL

Long-term Follow-up

- Adverse effects
- Infections
- Secondary malignancies

Long-Term Follow-up of Bendamustine-Treated Patients

- Retrospective analysis of 194 pts at GUH
- CLL and all lymphoma histologies
- Treatment from 2008-June 2015
- Evaluation using NCI-WG/Lugano Response
- Data extracted from EMR data base
- Median f/u – 31.2 (1.5-90.2) months

Penne et al, Clin Lymph Leuk Myeloma 17:637, 2017

Bendamustine Long-Term Follow-up

Bendamustine Detail	All Patients	Patients With CLL/SLL	Patients With Lymphoma	No. of First-Line Patients (%)	No. of Salvage Therapy Patients (%)
Median dosage, mg/m^2	90	70	90	90	90
Median cycles	6	6	6	6	5
Bendamustine regimen, no. of patients (%)					
Bendamustine	12 (6.2)	2 (3.2)	10 (7.6)	3 (2.9)	9 (8.6)
Bendamustine + rituximab	167 (86.1)	58 (92.1)	109 (83.2)	84 (80.0)	83 (79.0)
Bendamustine + rituximab + bortezomib	9 (4.6)	0 (0.0)	9 (6.9)	2 (1.9)	7 (6.7)
Bendamustine + lenalidomide	3 (1.5)	0 (0.0)	3 (2.3)	0 (0.0)	3 (2.9)
Bendamustine + ofatumumab	3 (1.5)	3 (4.8)	0 (0.0)	0 (0.0)	3 (2.9)

Penne et al, Clin Lymph Leuk Myeloma 17:637, 2017

Secondary Malignancies with Bendamustine (n=194)

New Secondary Malignancy	No. of Total Patients (%)	No. of Patients With CLL/SLL (%)	No. of Patients With Lymphoma (%)	No. of First-Line Patients (%)	No. of Salvage Therapy Patients (%)	During/Post-Bendamustine
Malignancies	21 (10.8)	10 (15.9)	11 (8.4)	7 (7.9)	14 (13.3)	13
Basal cell carcinoma	4 (2.1)	2 (3.2)	2 (1.5)	1 (1.1)	3 (2.9)	3
Bladder cancer	2 (1.0)	1 (1.6)	1 (0.8)	1 (1.1)	1 (1.0)	2
Hystiocytic carcinoma	1 (0.5)	0 (0.0)	1 (0.8)	0 (0.0)	1 (1.0)	0
Lung cancer	1 (0.5)	0 (0.0)	1 (0.8)	1 (1.1)	0 (0.0)	0
Melanoma	2 (1.0)	0 (0.0)	2 (1.5)	0 (0.0)	2 (1.9)	1
Prostate cancer	3 (1.5)	1 (1.6)	2 (1.5)	1 (1.1)	2 (1.9)	3
Renal cancer	3 (1.5)	2 (3.2)	1 (0.8)	1 (1.1)	2 (1.9)	1
Squamous cell	8 (4.1)	4 (6.3)	4 (3.1)	2 (2.2)	6 (5.7)	4

Penne et al, Clin Lymph Leuk Myeloma 17:637, 2017

Infections with Bendamustine (n=194)

Secondary Infection	No. of Total Patients (%)	No. of Patients With CLL/SLL (%)	No. of Patients With Lymphoma (%)	No. of First-Line Patients (%)	No. of Salvage Therapy Patients (%)
Infections	122 (62.9)	40 (63.5)	82 (62.6)	52 (58.4)	70 (66.7)
Serious					
Sepsis	2 (1.0)	2 (3.2)	0 (0.0)	1 (1.1)	1 (1.0)
Bacterial meningitis	1 (0.5)	0 (0.0)	1 (0.8)	0 (0.0)	1 (1.0)
Viral meningitis	1 (0.5)	0 (0.0)	1 (0.8)	1 (1.1)	0 (0.0)
Pneumonia	55 (28.4)	25 (39.7)	30 (22.9)	21 (23.6)	34 (32.4)
Other					
Cellulitis	27 (13.9)	10 (15.9)	17 (13.0)	11 (12.4)	16 (15.2)
Gastrointestinal	17 (8.8)	5 (7.9)	12 (9.2)	8 (9.0)	9 (8.6)
Genito-urinary	14 (7.2)	6 (9.5)	8 (6.1)	4 (4.5)	10 (9.5)
Herpes	30 (15.5)	12 (19.0)	18 (13.7)	7 (7.9)	23 (21.9)
MRSA	1 (0.5)	1 (1.6)	0 (0.0)	1 (1.1)	0 (0.0)
Otitis	3 (1.5)	1 (1.6)	2 (1.5)	0 (0.0)	3 (2.9)
PJP	2 (1.0)	1 (1.6)	1 (0.8)	0 (0.0)	2 (1.9)
Retinitis	1 (0.5)	0 (0.0)	1 (0.8)	0 (0.0)	1 (1.0)
Upper respiratory	53 (27.3)	18 (28.6)	35 (26.7)	26 (29.2)	27 (25.7)
Bacteremia	3 (1.5)	3 (4.8)	0 (0.0)	1 (1.1)	2 (1.9)

Penne et al, Clin Lymph Leuk Myeloma 17:637, 2017

Long-Term Follow-up Of Bendamustine Treated FL

- 149 pts on 3 clinical trials (2 SA, 1 BR)
- Median 5 prior therapies
- Median f/u 8.9 yrs
- Incidence of AML/MDS 0.5%/yr (6 MDS, 2AML)(cumulative 6.2%)
- Median time to AML/MDS 23 mo (10-103)
- Others: skin (6); colon, prostate, lung (2 each); hcc, bladder (1 each)

Martin et al Br J Haematol 178:250, 2017

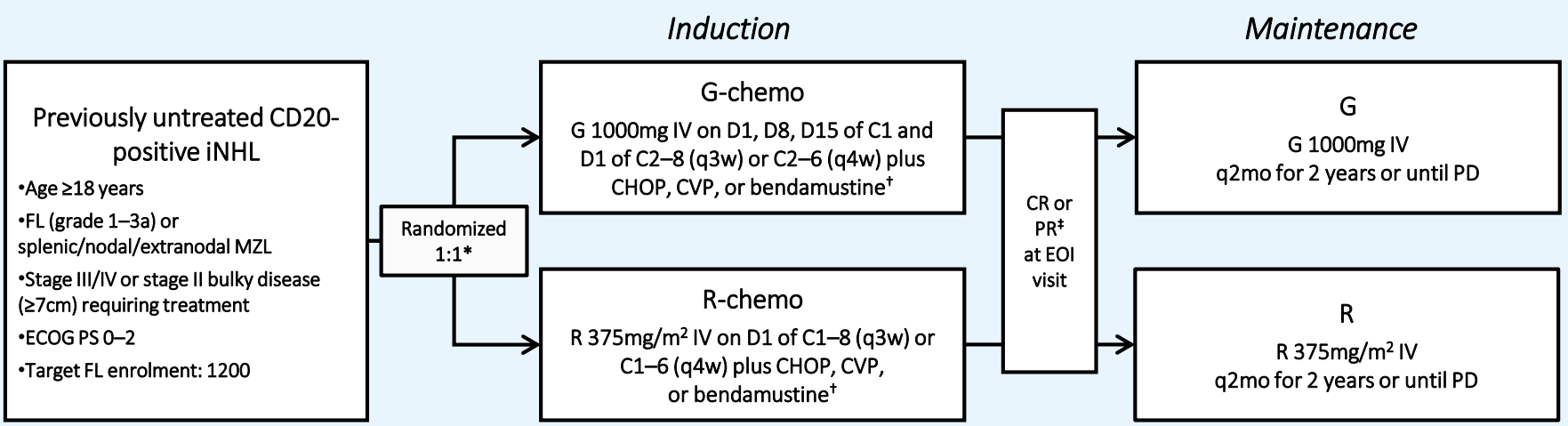
Long-Term Follow-up Of Bendamustine Treated FL

- 26 infections prior to next treatment
  - Sinopulmonary – 14
  - HSV/VZV – 6
  - Sepsis – 3
  - UTI - 3

Martin et al Br J Haematol 178:250, 2017

GALLIUM Study design

International, open-label, randomized Phase III study



Primary endpoint

- PFS (INV-assessed in FL)

Secondary and other endpoints

- PFS (IRC-assessed) §
- OS, EFS, DFS, DoR, TTNT
- CR/ORR at EOI (+/− FDG-PET)
- Safety

*FL and MZL pts were randomized separately; stratification factors: chemotherapy, FLIPI (FL) or IPI (MZL) risk group, geographic region; †CHOP q3w × 6 cycles, CVP q3w × 8 cycles, bendamustine q4w × 6 cycles; choice by site (FL) or by pt (MZL); ‡Pts with SD at EOI were followed for PD for up to 2 years; § Confirmatory endpoint

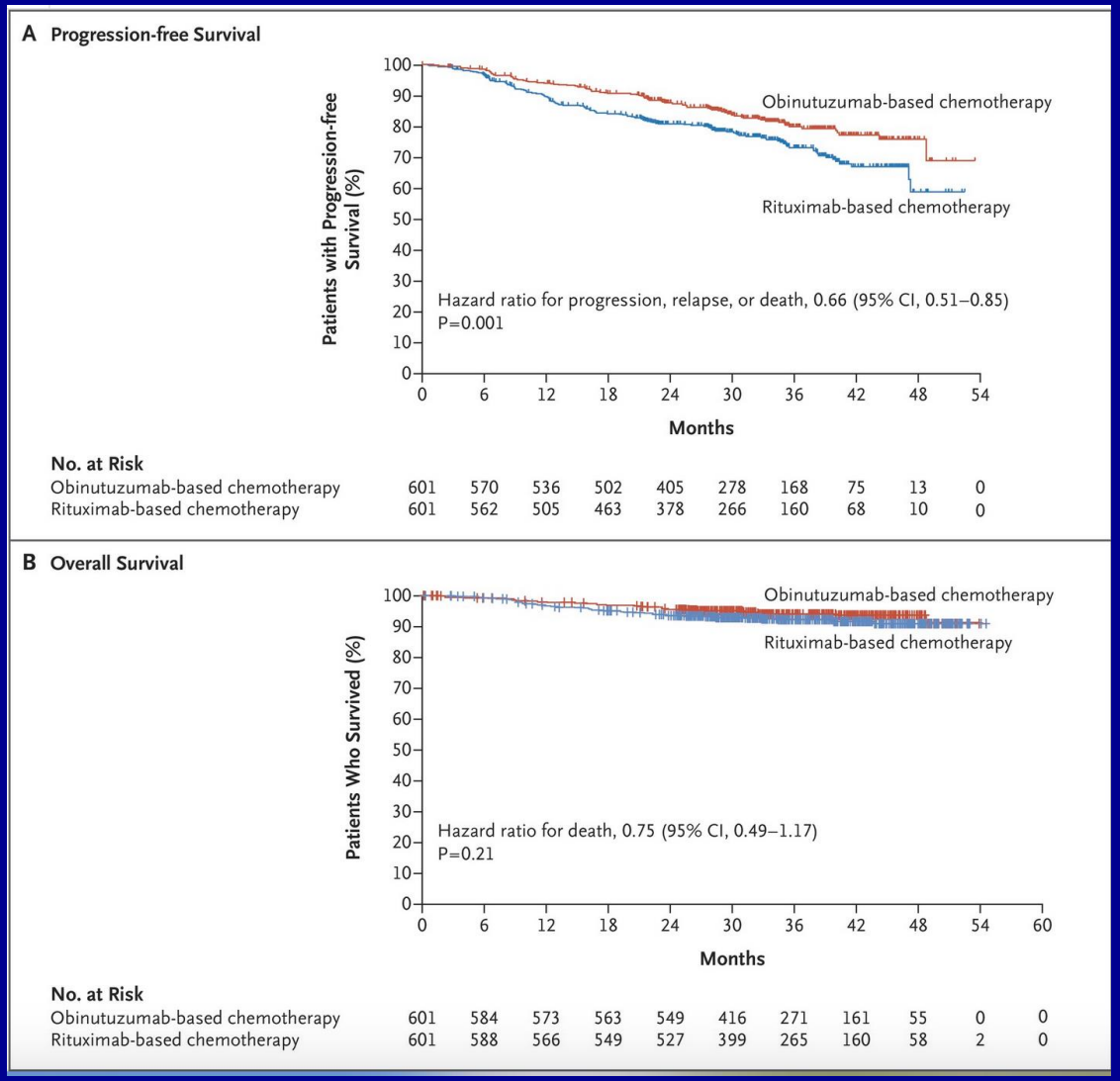
Marcus et al NEJM 377:1331, 2017

Baseline characteristics by chemo*

n (%)	*Benda, n=686*	*CHOP, n=399*	*CVP, n=117*
Median age, years (range)	59 (23–88)	58 (31–85)	59 (32–85)
Age ≥80 years	**23 (3.4)**	3 (0.8)	**4 (3.4)**
Male	332 (48.4)	177 (44.4)	54 (46.2)
Charlson Comorbidity Index score ≥1†	**163 (23.8)**	69 (17.3)	22 (18.8)
ECOG PS 2	24 (3.5)	8 (2.0)	6 (5.1)
FLIPI high risk (≥3)	274 (39.9)	**187 (46.9)**	41 (35.0)
Bulky disease (≥7cm)	274 (39.9)	**206 (51.6)**	46 (39.3)

*ITT population. †Scored retrospectively based on conditions reported on medical history page of CRF.

GALLIUM: PFS. OS

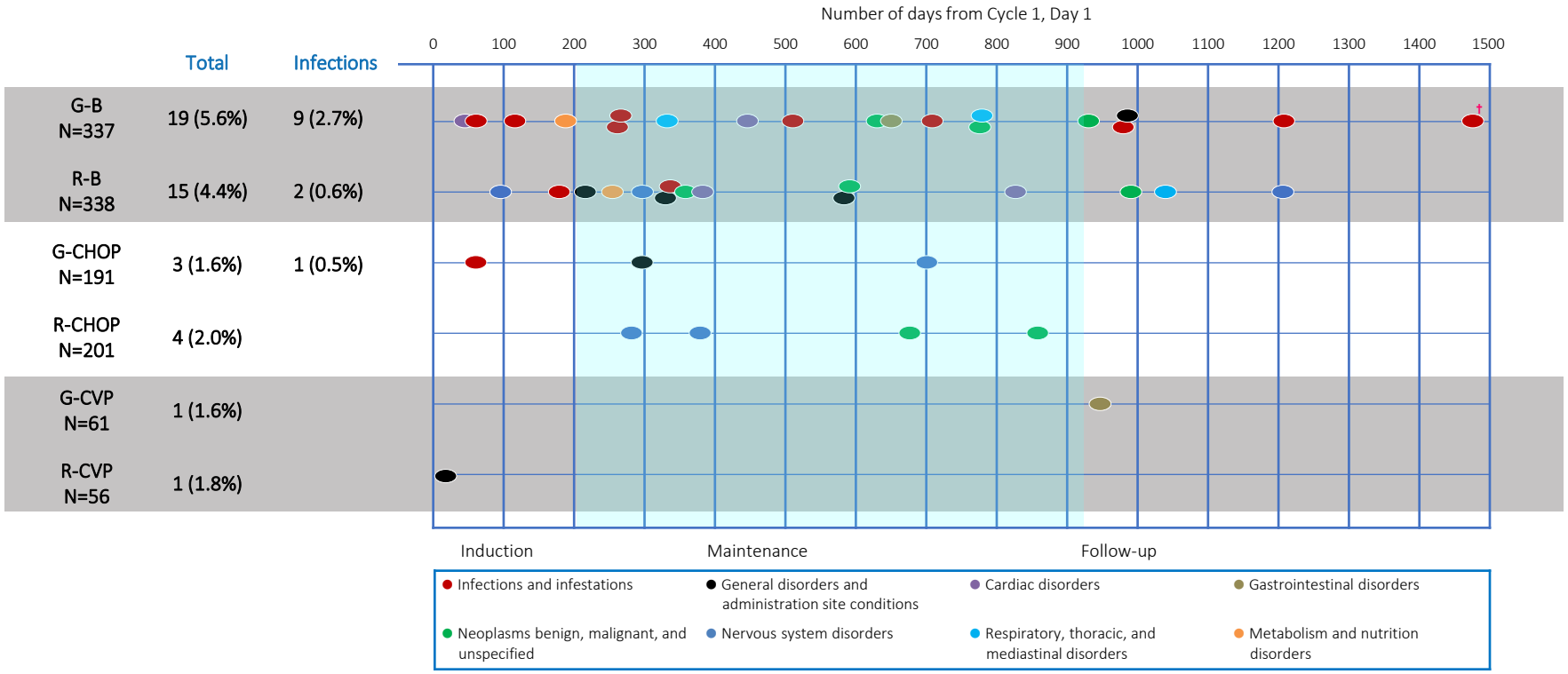


Marcus et al NEJM 377:1331, 2017

GALLIUM Toxicity

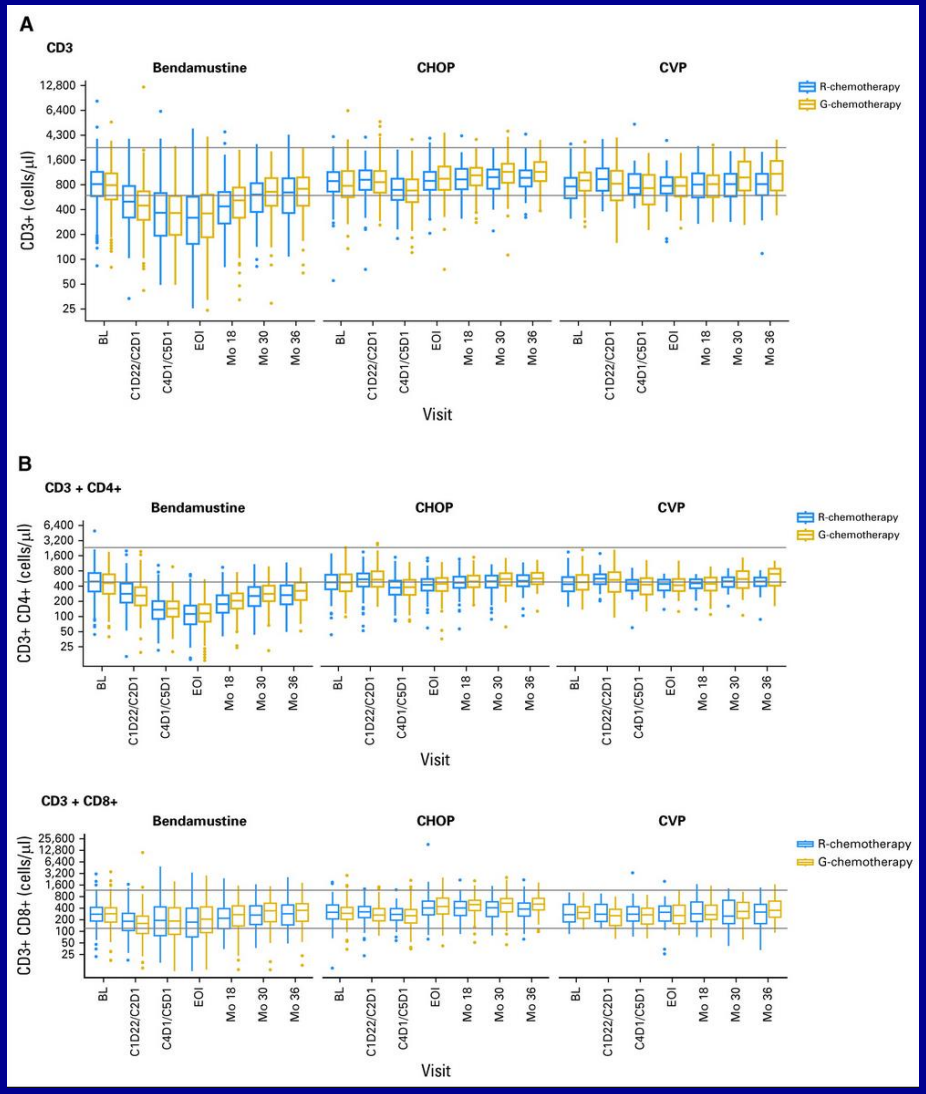
Event	Overall Trial†		Induction Phase		Maintenance and Observation Phases		Follow-up	
	Obinutuzumab Group (N=595)	Rituximab Group (N=597)	Obinutuzumab Group (N=595)	Rituximab Group (N=597)	Obinutuzumab Group (N=548)	Rituximab Group (N=535)	Obinutuzumab Group (N=427)	Rituximab Group (N=428)
No. of events	10,311	9343	7012	6533	3002	2578	295	230
Patients with ≥1 adverse event — no. (%)								
Any event	592 (99.5)	587 (98.3)	580 (97.5)	577 (96.6)	501 (91.4)	458 (85.6)	130 (30.4)	106 (24.8)
Event of grade 3 to 5	444 (74.6)	405 (67.8)	357 (60.0)	336 (56.3)	205 (37.4)	169 (31.6)	56 (13.1)	33 (7.7)
Event of grade 5‡	24 (4.0)	20 (3.4)§	4 (0.7)	3 (0.5)	10 (1.8)	10 (1.9)	10 (2.3)	7 (1.6)
Patients with ≥1 serious adverse event — no. (%)	274 (46.1)	238 (39.9)	166 (27.9)	144 (24.1)	134 (24.5)	110 (20.6)	47 (11.0)	34 (7.9)
Grade 3 to 5 event, according to chemotherapy regimen — no./total no. (%)								
Neutropenia	—	—						
Bendamustine	—	—	73/338 (21.6)	87/338 (25.7)	49/312 (15.7)	29/305 (9.5)	6/270 (2.2)	1/263 (0.4)
CHOP	—	—	124/193 (64.2)	103/203 (50.7)	36/179 (20.1)	26/187 (13.9)	2/128 (1.6)	0
CVP	—	—	24/61 (39.3)	13/56 (23.2)	5/57 (8.8)	2/43 (4.7)	0	0
Infection¶	—	—						
Bendamustine	—	—	27/338 (8.0)	26/338 (7.7)	52/312 (16.7)	39/305 (12.8)	25/270 (9.3)	6/263 (2.3)
CHOP	—	—	14/193 (7.3)	13/203 (6.4)	7/179 (3.9)	11/187 (5.9)	2/128 (1.6)	2/143 (1.4)
CVP	—	—	3/61 (4.9)	4/56 (7.1)	5/57 (8.8)	1/43 (2.3)	1/44 (2.3)	2/45 (4.4)
Second neoplasm‖	—	—						
Bendamustine	—	—	0	0	21/312 (6.7)	18/305 (5.9)	14/270 (5.2)	2/263 (0.8)
CHOP	—	—	0	0	8/179 (4.5)	8/187 (4.3)	1/128 (0.8)	1/143 (0.7)
CVP	—	—	0	0	0	1/43 (2.3)	0	0

Grade 5 (fatal) AEs by treatment (FL)*



*Includes only pts who died before clinical cut-off date; †this patient (G-B group) was initially assigned three causes of death (*Clostridium difficile* colitis, prostate cancer, and myelodysplastic syndrome); *Clostridium difficile* colitis was the most acute, so the patient has been assigned to the 'Infections and infestations' category and the number of fatal AEs in G-B pts in neoplasms SOC reduced from 5 to 3

GALLIUM: T-cell Subsets



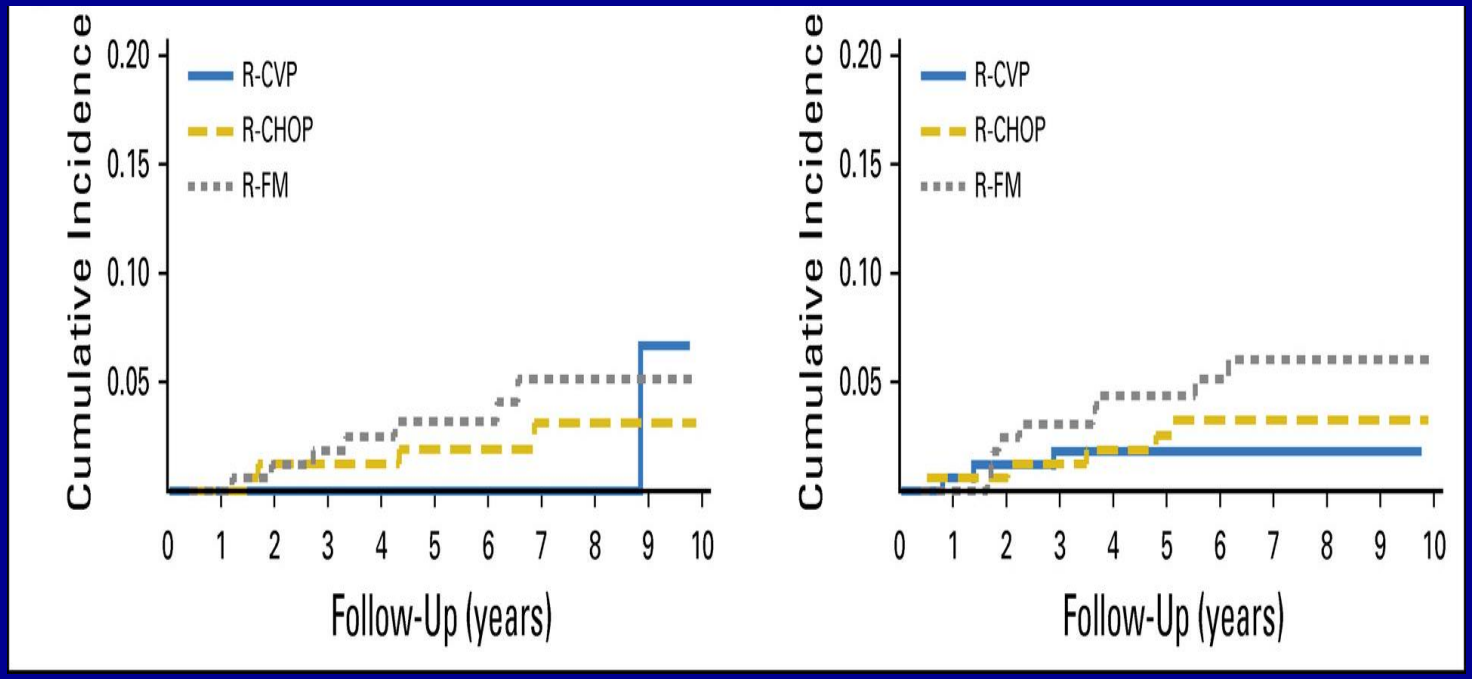
Hiddemann et al JCO 36:2395, 2018

Grade 3–5 and fatal AEs in Gallium vs other studies of R or G + chemo

n (%) of pts reporting ≥1 event	*Grade 3–5 AEs*	*Grade 3–5 infections*	*Grade 5 AEs*	*Grade 5 infections*
GALLIUM (BO21223)				
R-B (N=338)	228 (67.5)	66 (19.5)	16 (4.7)	2 (0.6)
G-B (N=338)	233 (68.9)	89 (26.3)	20 (5.9)	8 (2.4)
R-CHOP (N=203)	151 (74.4)	25 (12.3)	4 (2.0)	0 (0.0)
G-CHOP (N=193)	171 (88.6)	23 (11.9)	3 (1.6)	1 (0.5)
R-CVP (N=56)	30 (53.6)	7 (12.5)	1 (1.8)	0
G-CVP (N=61)	42 (68.9)	8 (13.1)	1 (1.6)	0
SABRINA (BO22334)				
IV (N=210)	116 (55)	29 (13.8)	12 (5.7)	6 (2.9)
SC (N=197)	111 (56)	29 (14.7)	7 (3.6)	1 (0.5)
GOYA (BO21005)				
R-CHOP (N=703)	455 (64.7)	109 (15.5)	30 (4.3)	12 (1.7)
G-CHOP (N=704)	519 (73.7)	135 (19.2)	41 (5.8)	16 (2.3)

- Frequency of severe and fatal AEs (and infections) in GALLIUM is similar to previous results for the same or similar antibody–chemotherapy combinations

Long-term follow-up FOLLO-5



Second cancer NLR COD

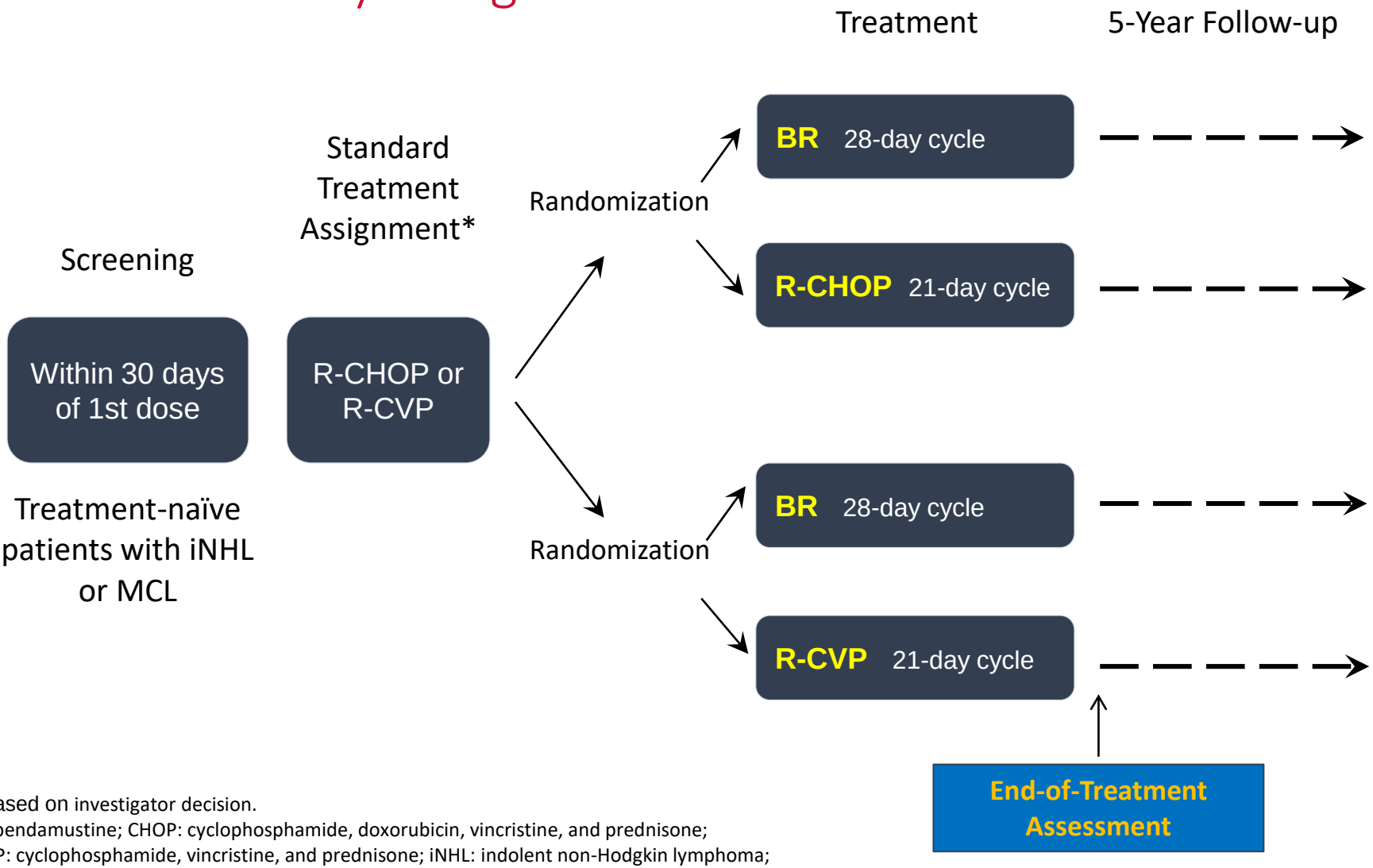
Other NLR COD

Luminari, et al, *JCO* 36:689, 2018.

Issues With GALLIUM

- More toxicity with BO
- Pts not randomized
- Groups were not balanced
- Majority received bendamustine
- Benda pts – older, more comorbidities
  - Death rate higher in these pts
- Most events during maintenance (R=O)
- Difference disappeared in patients <70 yrs

BRIGHT Study Design



*Based on investigator decision.
B: bendamustine; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP: cyclophosphamide, vincristine, and prednisone; iNHL: indolent non-Hodgkin lymphoma; MCL: mantle cell lymphoma; R: rituximab

Demographics/Disease Characteristics

Characteristic		BR (n = 224)	R-CHOP/R-CVP (n = 223)
Age, years, median (range)		60 (28-84)	58 (25-86)
Male, %		61	59
ECOG, %	0	64	64
	1	31	31
	2	4	4
Lymphoma type, %	Indolent NHL	83	83
	MCL	16	17
	Missing	<1	<1
Ann Arbor stage, %	II	9	9
	III	21	22
	IV	69	68
Median time from diagnosis to randomization, months, median (range)		1.55 (0.1-266.7)	0.80 (0.1-86.2)
FLIPI risk, %*	Low	14	14
	Intermediate	25	25
	High	29	33

*BR (n = 154); R-CHOP/R-CVP (n = 160).

BRIGHT Efficacy Summary (All Patients)

	BR	R-CHOP/R-CVP
Primary endpoint*		
Evaluable, n	213	206
CR	31%	25%
CR rate ratio	1.26; *P* = 0.0225 for non-inferiority	
5-year follow-up^		
Intent-to-treat, n	224	223
PFS	65.5%	55.8%
	HR = 0.61 (95% CI 0.45-0.85; *P* = 0.0025)	
OS	81.6%	85.0%
	HR = 1.15 (95% CI 0.72-1.84; *P* = 0.5461)	

**Blood*. 2014;123(19):2944-2952; powered for non-inferiority of CR ratio.
^Flinn IW, et al. ASCO 2017. P7500.
B: bendamustine; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; CI: confidence interval; CR: complete response; CVP: cyclophosphamide, vincristine, and prednisone; HR: hazard ratio; OS: overall survival, PFS: progression-free survival; R: rituximab

Adverse Events (all grades)

- BR was associated with a higher incidence of nausea and vomiting, pyrexia, chills, drug hypersensitivity, decreased appetite, rash, and pruritus
- R-CHOP and R-CVP were associated with a higher incidence of constipation, paresthesia, peripheral neuropathy, and alopecia
- R-CHOP was associated with a higher incidence of febrile neutropenia and mucosal inflammation

Supportive Care

	Preassigned to R-CHOP		Preassigned to R-CVP	
Supportive Care (%)	**BR (n = 103)**	**R-CHOP (n = 98)**	**BR (n = 118)**	**R-CVP (n = 116)**
Any	27	63	33	31
Red blood cells/platelets (transfusion products)	4	7	5	7
Erythropoietin	<1	7	3	2
Colony-stimulating growth factors*	27	61	30	27

*Per institutional standards.

■ = Higher incidence.

Adverse Events in during induction *

n (%)	R-CHOP/R-CVP (n = 144)		BR (n = 144)	
	Maintenance R (n = 83)	No Maintenance R (n = 61)	Maintenance R (n = 81)	No Maintenance R (n = 63)
Any adverse event	83 (100)	61 (100)	81 (100)	63 (100)
Grade ≥3 adverse event	45 (54)	40 (66)	48 (59)	35 (56)
Serious adverse events (SAEs)	15 (18)	13 (21)	19 (23)	20 (32)
SAEs occurring in >2 pts				
Febrile neutropenia	3 (4)	2 (3)	3 (4)	1 (2)
Neutropenia	1 (1)	1 (2)	3 (4)	0
Pyrexia	3 (4)	0	1 (1)	4 (6)
Pneumonia	0	0	1 (1)	3 (5)
SAEs of interest by SOC				
Infections, infestations	0	3 (5)	5 (6)	8 (13)
Secondary malignancies	1 (1)	0	0	1 (2)

*Adverse events were only collected during BR or R-CHOP/R-CVP study period, and not during maintenance therapy or long-term follow-up. Includes FL patients with CR or PR.

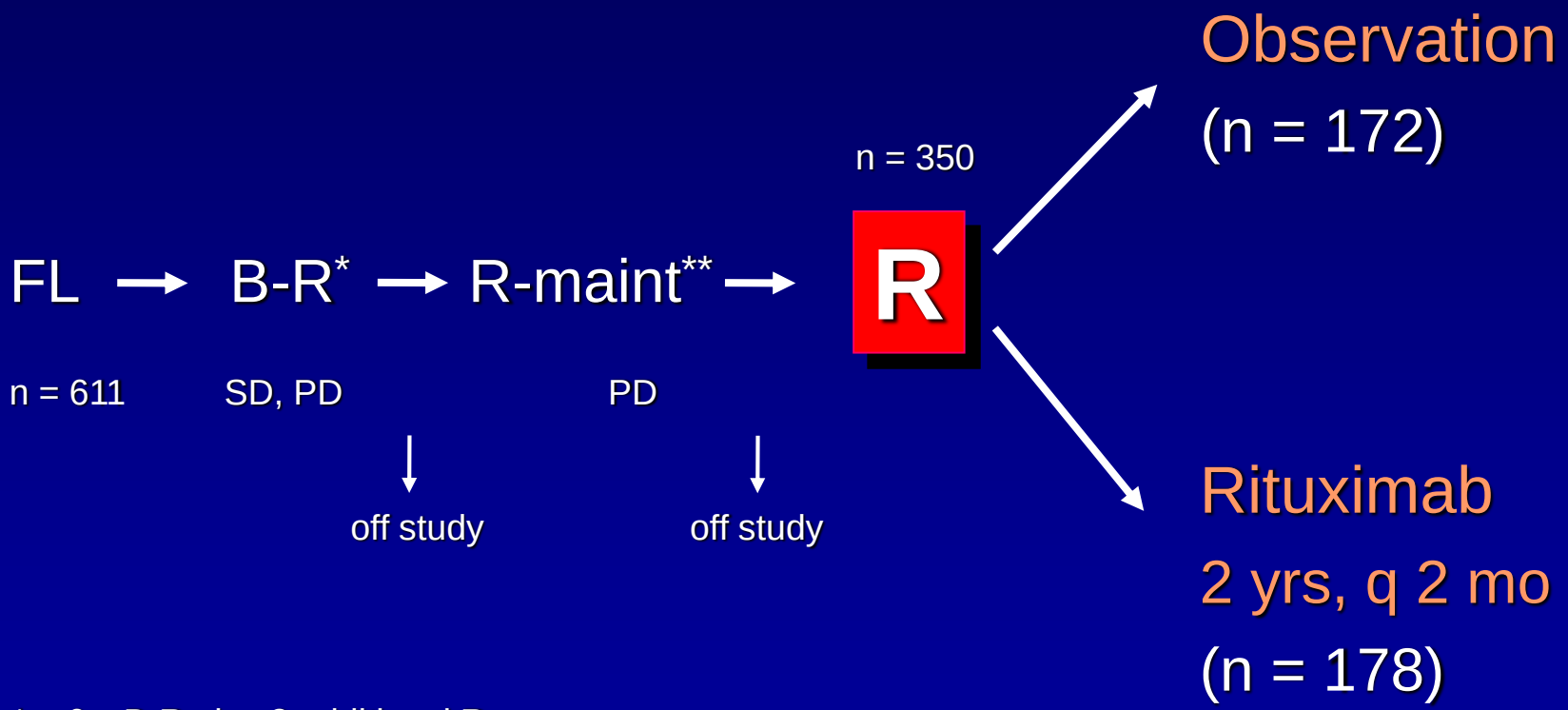
Secondary Malignancy*

	BR (n = 221)	R-CHOP/R-CVP (n = 215)	
Transformed NHL/DLBCL	5	7	
Basal cell carcinoma	9	4	
Squamous carcinoma of the skin	12	2	
Melanoma	2	1	
MDS	1	1	
Other solid malignancy	19	11	
Patients with secondary malignancy	42 (19%)	24 (11%)	*P* = 0.022
Excluding NHL and non-melanoma skin cancer	22 (10%)	13 (6%)	*P* = 0.133

*Exploratory analysis; histology not collected.
DLBCL: diffuse large B-cell lymphoma; MDS: myelodysplastic syndrome.

B-R + 2 years versus B-R + 4 years Rituximab

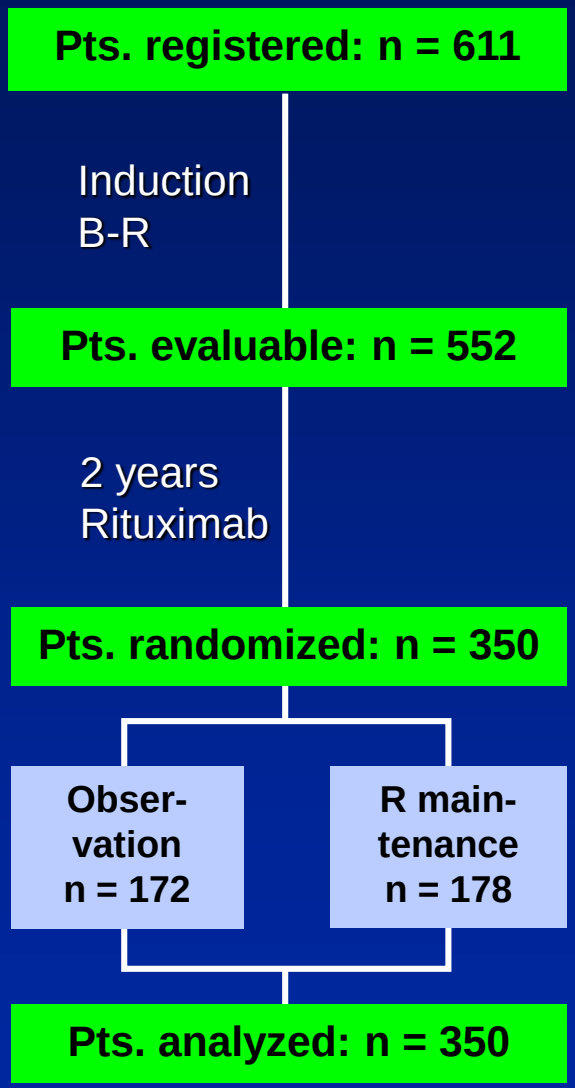
StiL NHL 7-2008 - MAINTAIN



* 6 x B-R plus 2 additional R

** R-maintenance q 2 months for 2 years

Patient disposition - Reasons for non-randomization



261 (42.6%) Patients not randomized		Induct	2 yrs R
Death	11 (4%)	7	4
PD / SD	63 (24%)	10 / 7	46 / -
Transformation	26 (10%)	15	11
Intolerance R / B	15 (6%)	8 / 4	3 / -
Withdrawn consent	39 (15%)	12	27
Protocol violation	26 (10%)	7	19
Neutropenia / Cytopenia	21 (8%)	2	19
Infections	9 (3%)	-	9
Secondary malignancy	16 (6%)	3	13
Other histology	8 (3%)	8	-
Other reasons	27 (10%)	5	22

Rummel et al. Blood 2017; 130: 483

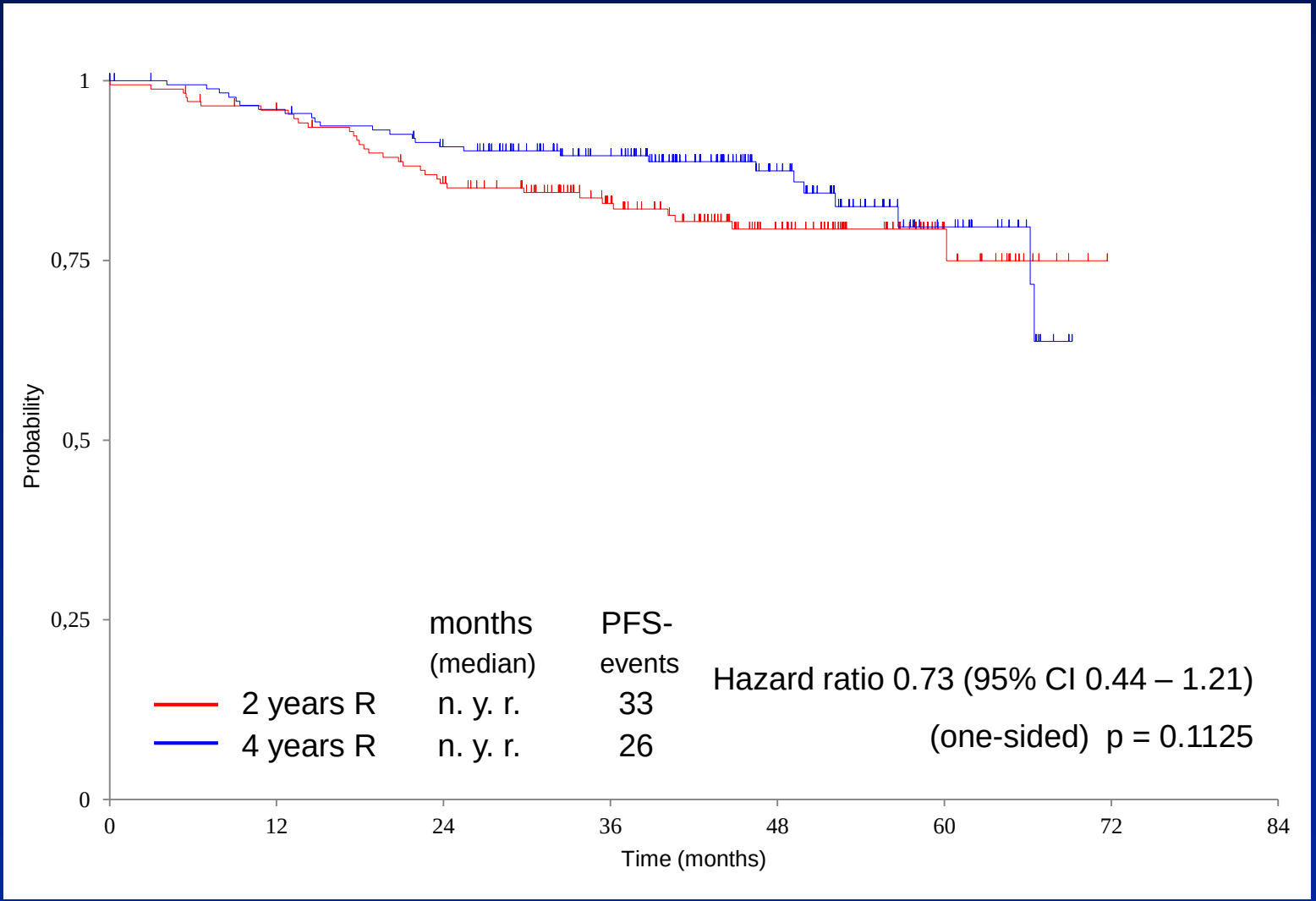
Response rates following B-R induction

552 patients available for response evaluation

ORR	90%
CR	28%
PR	61%
SD	6%
PD	5%
e.d.	1%

Rummel et al. Blood 2017; 130: 483

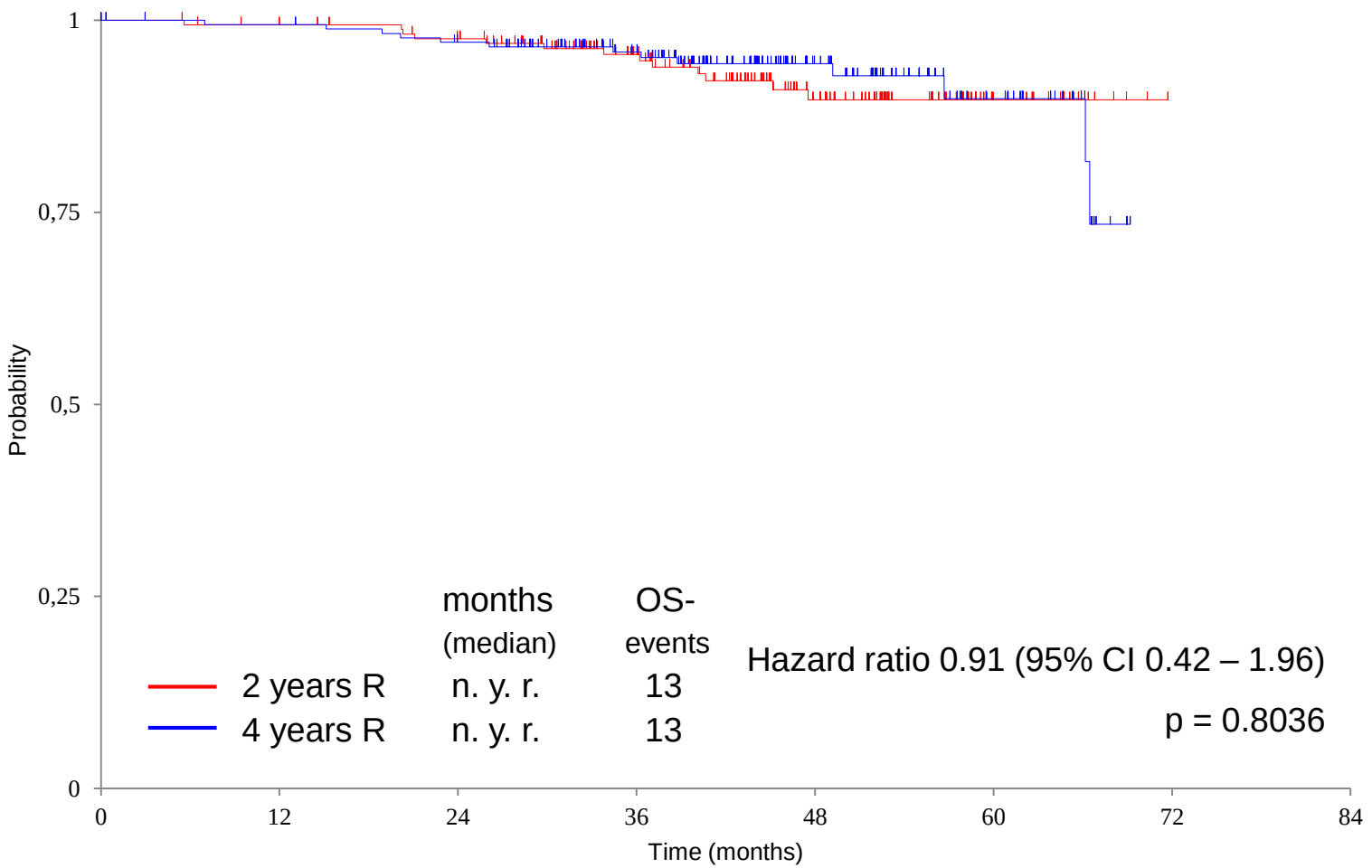
Progression-free survival from randomization (n = 350)



Pts at risk					
Observation	172	161	141	106	62
R-maintenance	178	168	155	123	61

Rummel et al. Blood 2017; 130: 483

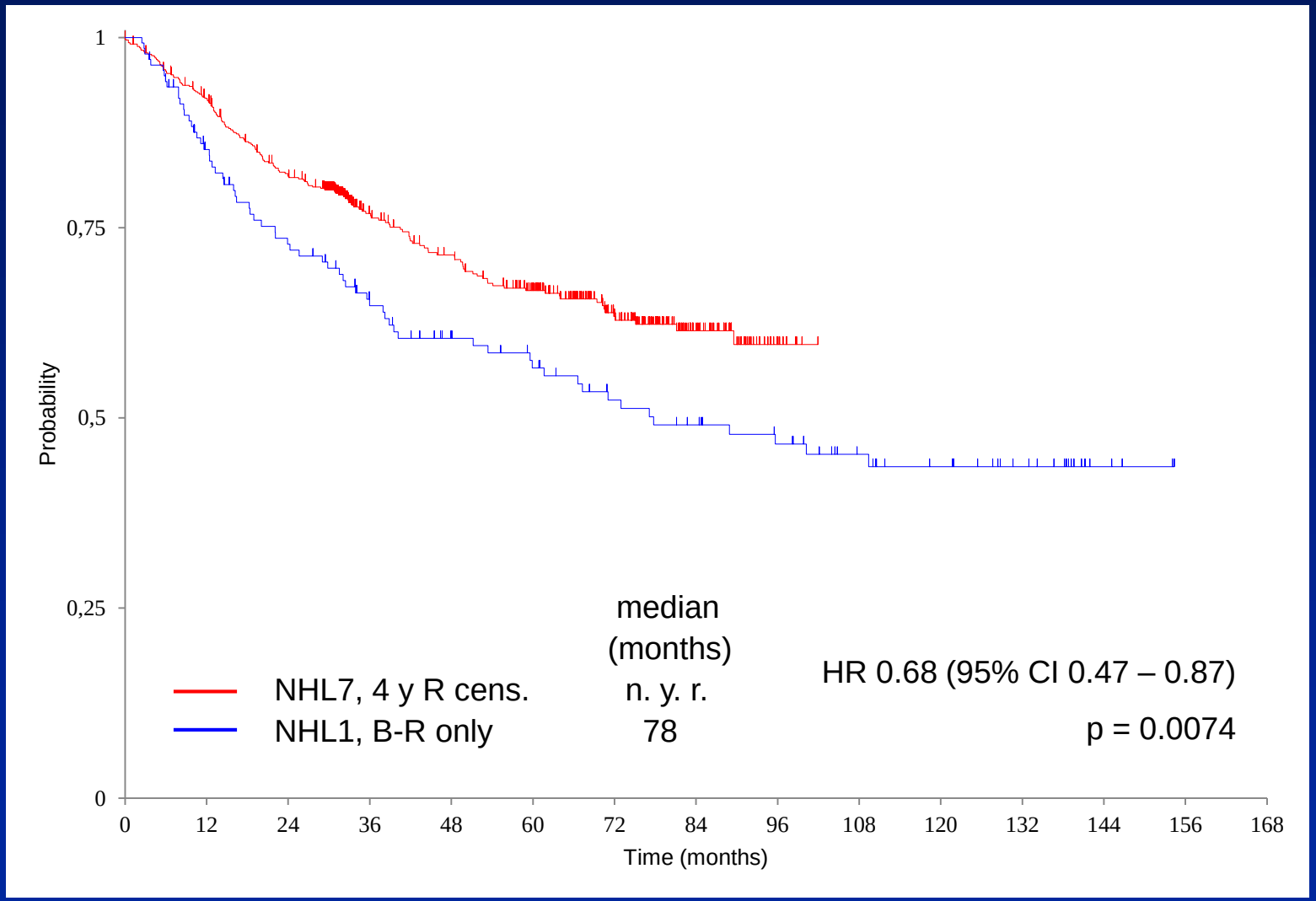
Overall survival from randomization



Pts at risk					
Observation	172	166	159	120	67
R-maintenance	178	174	167	135	65

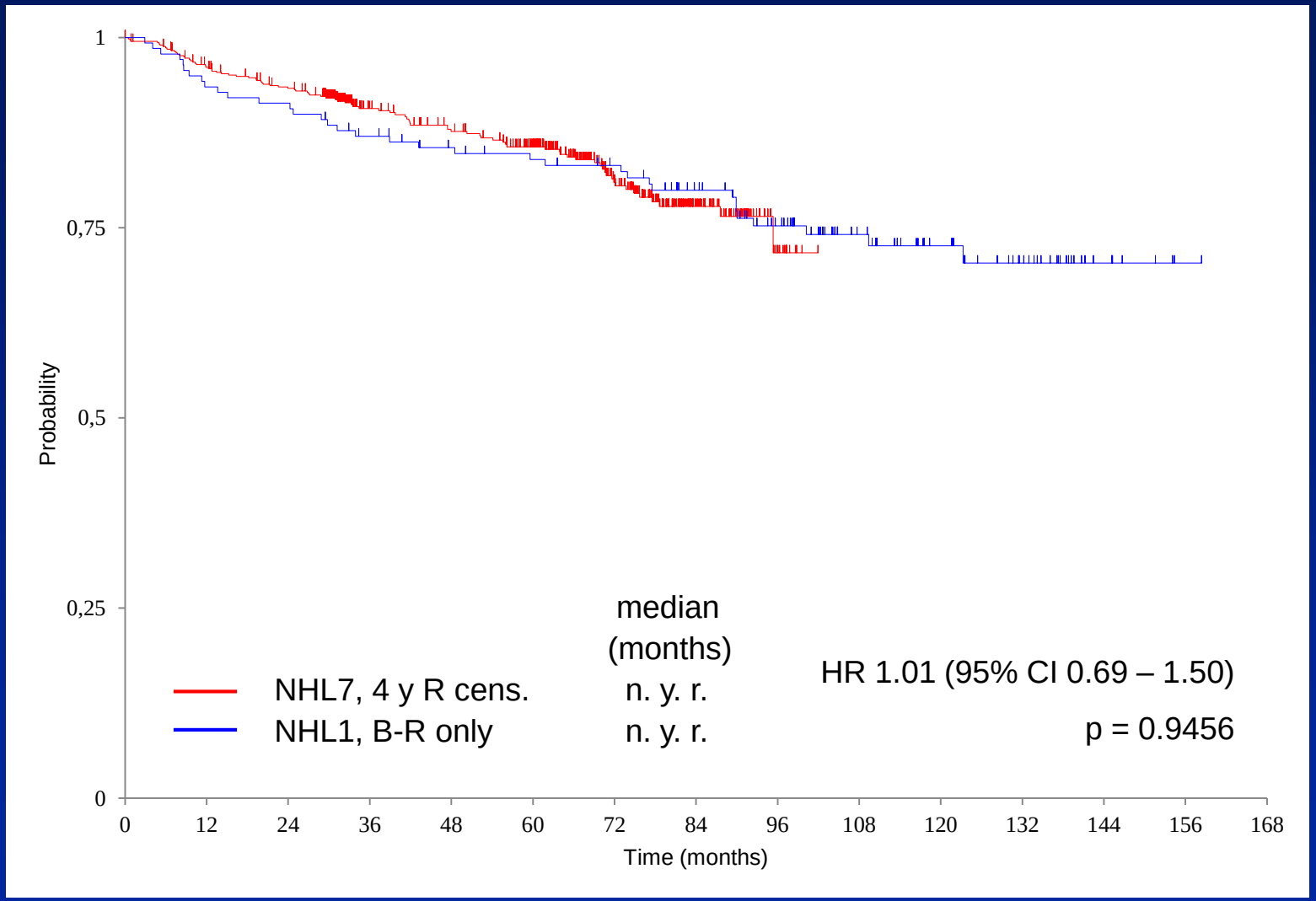
Rummel et al. Blood 2017; 130: 483

PFS comparison: NHL 1 (B-R, foll.) vs. NHL 7 (4y R cens.)



Rummel et al. Blood 2017; 130: 483

OS comparison: NHL 1 (B-R, foll.) vs. NHL 7 (4y R cens.)



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Toxicity grade 3/4 per pts during induction + 2 yrs R

	2 yrs R (n = 172)	4 yrs R (n = 178)	not rand (n = 261)	all patients (n = 595)
Neutropenia	35 (20%)	31 (17%)	41 (16%)	107 (18%)
Leukopenia	17 (10%)	19 (11%)	26 (10%)	62 (10%)
Thrombocytopenia	-	1 (1%)	2 (1%)	3 (1%)
GOT / GPT /GGT	1 (1%)	3 (2%)	2 (1%)	6 (1%)
Other lab. anomalies	5 (3%)	7 (4%)	10 (4%)	22 (4%)
Infections	11 (6%)	5 (3%)	25 (10%)	**41 (7%)**
Pneumonia	6 (3%)	4 (2%)	17 (7%)	**27 (5%)**
Cardiac events	4 (2%)	3 (2%)	13 (5%)	20 (3%)
Gastrointestinal	7 (4%)	6 (3%)	12 (5%)	25 (4%)
Inflammation	2 (1%)	3 (2%)	6 (2%)	11 (2%)
Dyspnea	-	4 (2%)	7 (3%)	11 (2%)
Diarrhea	1 (1%)	2 (1%)	10 (4%)	13 (2%)
Allergy	-	0 (0%)	7 (3%)	7 (1%)
Chill / fever	5 (3%)	8 (4%)	10 (4%)	23 (4%)
Pain	2 (1%)	4 (2%)	7 (3%)	13 (2%)

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Toxicity grade 3/4 per pts after randomization

	2 yrs R (n = 172)	4 yrs R (n = 178)	Random. pts (n = 350)
Neutropenia	17 (10%)	12 (7%)	29 (8%)
Leukopenia	8 (5%)	6 (3%)	14 (4%)
Thrombocytopenia	0 (0%)	2 (1%)	2 (0%)
GOT / GPT /GGT	2 (1%)	2 (1%)	4 (1%)
Other lab. anomalies	8 (5%)	6 (3%)	14 (4%)
Infections	**10 (6%)**	**4 (2%)**	**14 (4%)**
Pneumonia	**9 (5%)**	**4 (2%)**	**13 (4%)**
Cardiac events	10 (6%)	5 (3%)	15 (4%)
Gastrointestinal	7 (4%)	4 (2%)	11 (3%)
Inflammation	3 (2%)	1 (1%)	4 (1%)
Dyspnea	4 (2%)	0 (0%)	4 (1%)
Diarrhea	0 (0%)	1 (1%)	1 (0%)
Allergy	-	-	-
Chill / fever	1 (1%)	1 (1%)	2 (0%)
Pain	2 (1%)	3 (2%)	5 (1%)

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Causes of death

	all patients (n = 595)	2 years R (n = 172)	4 years R (n = 178)
Death	103 (17.3%)	13 (7.6%)	13 (7.3%)
Lymphoma	32 (5.4%)	1 (<1%)	1 (<1%)
Infection	17 (2.8%)	1 (<1%)	3 (1.7%)
Cytopenia	1 (<1%)	-	-
Hepatitis reactivation	1 (<1%)	-	-
Cardiac reasons	5 (1%)	2 (1.2%)	-
Second malignancy	15 (2.5%)	3 (1.7%)	-
Other / unknown	32 (5.4%)	6 (3.5%)	9 (5.1%)

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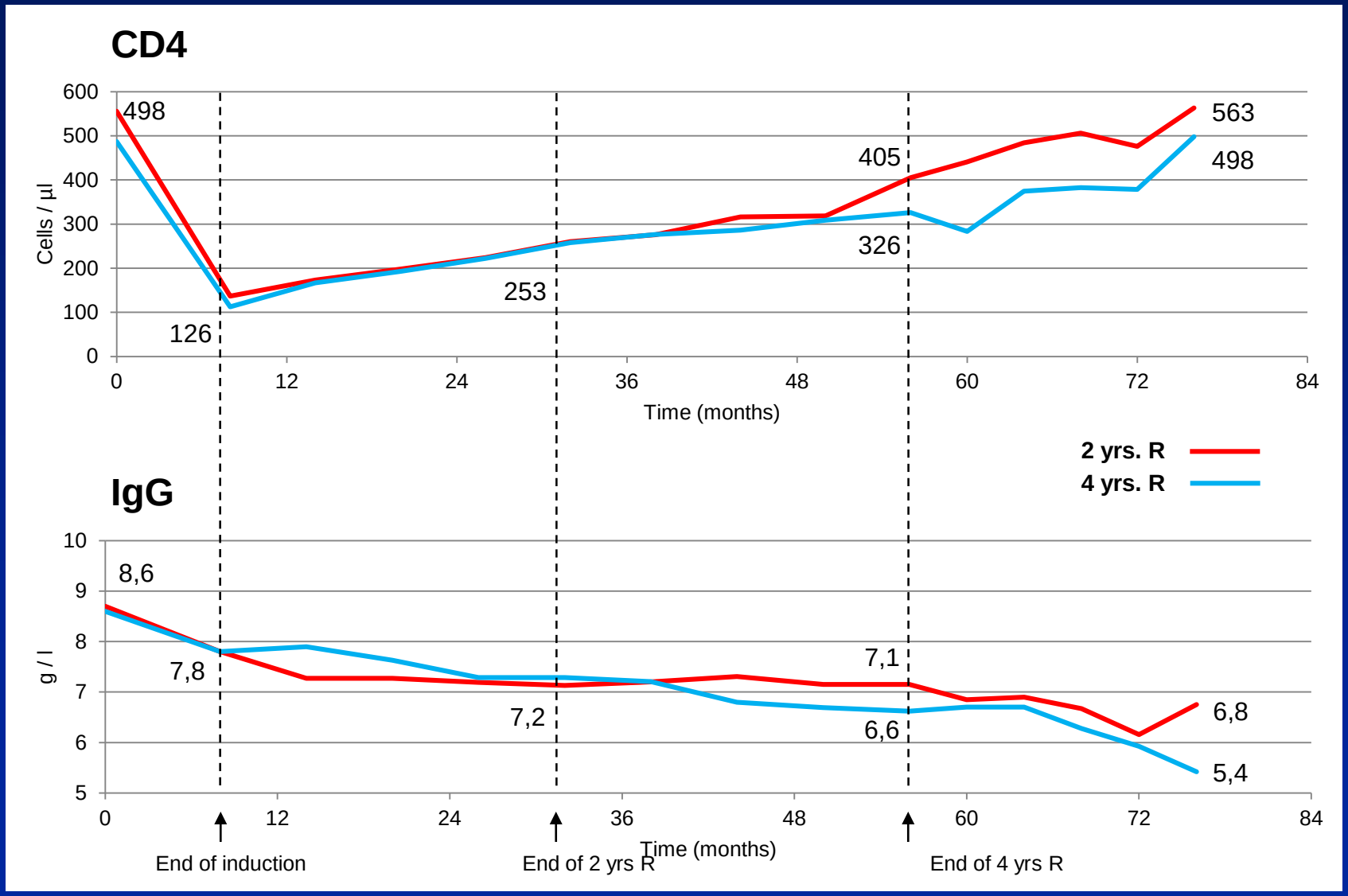
Fatal infections (75 months follow-up)

- 17 pts (2.8%) died from infection (13 not rand., 1 in 2 yrs, 3 in 4 yrs)
- Median age at registration: 71 years
- 9 died after a relapse and a 2nd-line treatment
- 7 were primary refractory and died early due to an infection
- 10 died in ongoing remission
- Infections:
  - 8 Pneumonia
  - 6 Sepsis
  - 1 Fungal infection
  - 1 PcP (72 yrs, 5 cycles B-R, died at the end of induction after 5 mo.)
  - 1 PML (41 yrs, 19 cycles R-maint., ongoing remission, on tx 3 ½ yrs)

CD4 and IgG



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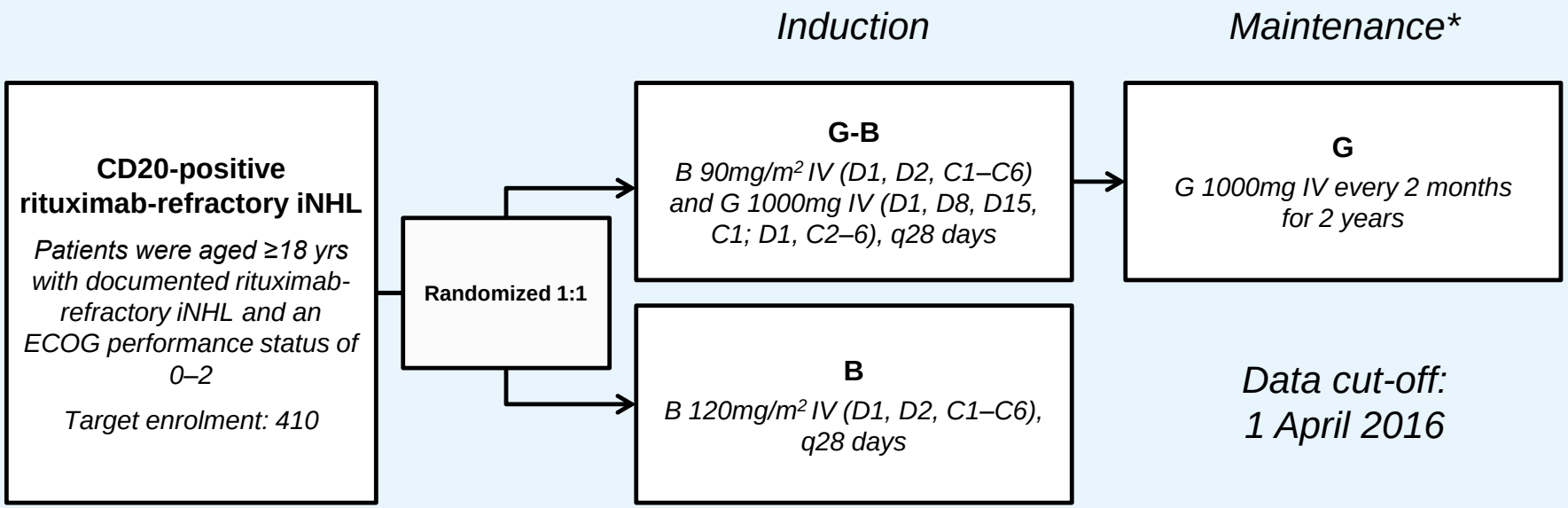
GADOLIN Study design

Open-label, multicenter, randomized, Phase III study in rituximab-refractory iNHL patients



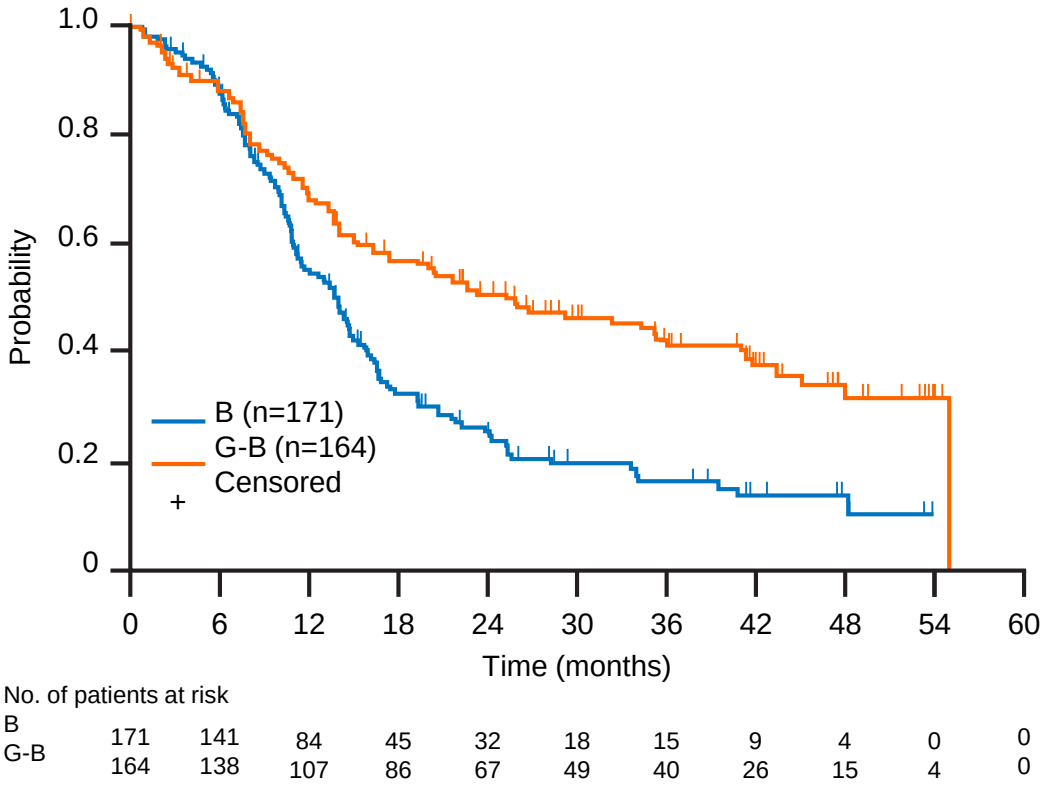
- **Rituximab-refractory definition:** Failure to respond to, or progression during any prior rituximab-containing regimen (monotherapy or combined with chemotherapy), or progression within 6 months of the last rituximab dose, in the induction or maintenance settings
- **Endpoints considered in current analysis:** PFS (INV), OS, TTNT, safety

Cheson et al JCO 36:2259, 2018

*Patients in the G-B arm without evidence of progression following induction received G maintenance

INV-assessed PFS in the FL population

Kaplan-Meier plot of INV-assessed PFS by treatment arm (FL)



	G-B, n=164	B, n=171
Pts with event, n (%)	93 (56.7)	125 (73.1)
Median PFS (95% CI), mo	25.3 (17.4, 36.0)	14.0 (11.3, 15.3)
HR (95% CI), p-value*	0.52 (0.39, 0.69), p<0.0001	

Median follow-up (FL): 31.2 months
(vs 21.1 months in primary analysis)

*Stratified analysis; stratification factors: prior therapies, refractory type, geographical region

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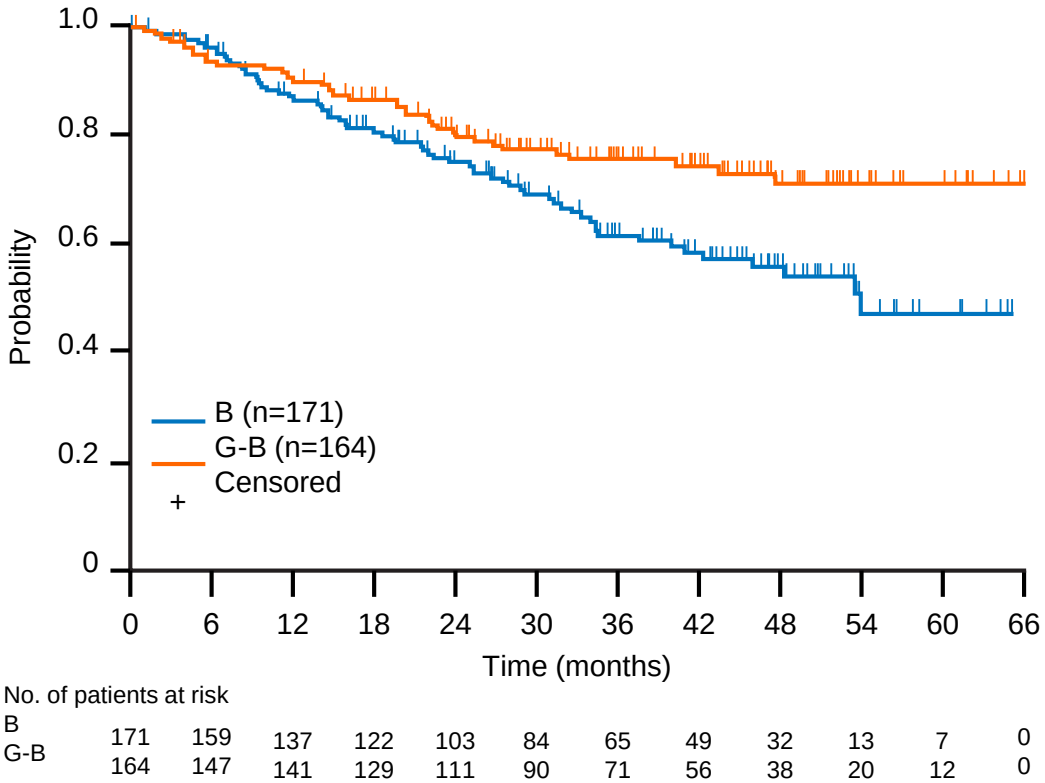
OS in the FL population

Kaplan-Meier plot of OS by treatment arm (FL)



	G-B, n=164	B, n=171
Pts with event, n (%)	39 (23.8)	64 (37.4)
Median OS (95% CI), mo	NR (NR, NR)	53.9 (40.9, NR)
HR (95% CI), p-value*	0.58 (0.39, 0.86), p=0.0061	

Median follow-up (FL): 31.2 months
(vs 21.1 months in primary analysis)

NR, not reached
*Stratified analysis; stratification factors: prior therapies, refractory type, geographical region

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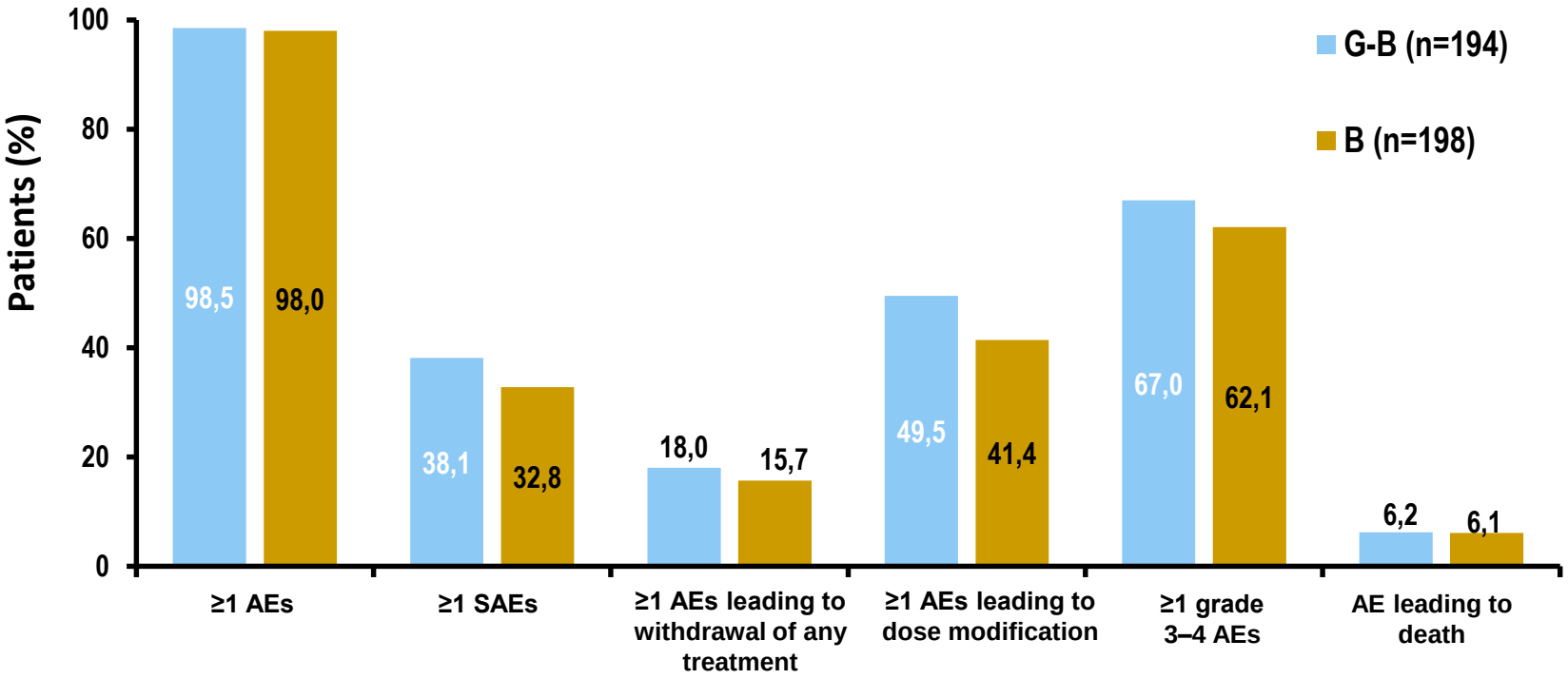
GADOLIN: Overview of AEs



AE, adverse event; SAE, serious adverse event

Adverse events in the iNHL population

% (n)	*G-B, n=204*	*B, n=203**
Any AE	99.0 (202)	98.5 (200)
Grade 3–5 AE	72.5 (148)	65.5 (133)
Grade 5 (fatal) AE	7.8 (16)	6.4 (13)
SAE	43.6 (89)	36.9 (75)
AE leading to withdrawal from any study treatment	20.1 (41)	17.2 (35)
AE leading to dose modification†	50.0 (102)	42.4 (86)

- Grade 5 (fatal) AEs listed by System Organ Class
  - G-B: infections and infestations, 6; neoplasms benign, malignant and unspecified, 5; blood and lymphatic system disorders, 1; cardiac disorders, 1; immune system disorders, 1; injury, poisoning and procedural complications, 1; renal and urinary disorders, 1
  - B: infections and infestations, 7; neoplasms benign, malignant and unspecified, 3; nervous system disorders, 2; metabolism and nutrition disorders, 1

*2 patients who crossed over from the B arm to the G-B arm during maintenance are excluded; †decrease or delay

Grade 3–5 adverse events in the iNHL population

Grade 3–5 AEs occurring with ≥5% incidence rate in either treatment arm at PT level

% (n)	*G-B, n=204*	*B, n=203**
Neutropenia	34.8 (71)	27.1 (55)
Thrombocytopenia	10.8 (22)	15.8 (32)
Anemia	7.4 (15)	10.8 (22)
Infusion-related reaction	9.3 (19)	3.4 (7)
Febrile neutropenia	5.9 (12)	3.4 (7)
Pneumonia	2.9 (6)	5.9 (12)

*2 patients who crossed over from the B arm to the G-B arm during maintenance are excluded

Grade 3–5 adverse events in the iNHL population

Grade 3–5 AEs of interest by treatment arm and treatment phase

	Induction		Maintenance	Overall	
% (n)	G-B, n=204	B, n=205†	G-B, n=158*	G-B, n=204	B, n=203*
Neutropenia‡	27.5 (56)	26.8 (55)	10.8 (17)	34.8 (71)	27.1 (55)
Thrombocytopenia‡	10.3 (21)	15.6 (32)	1.3 (2)	10.8 (22)	15.8 (32)
Infections and infestations§	7.8 (16)	12.2 (25)	10.1 (16)	22.5 (46)	19.2 (39)
Infusion-related reactions‡	8.8 (18)	3.4 (7)	0.6 (1)	9.3 (19)	3.4 (7)
Neoplasms§¶	1.0 (2)	1.0 (2)	2.5 (4)	5.9 (12)	5.4 (11)
Cardiac disorders§**	2.5 (5)	1.0 (2)	1.9 (3)	4.4 (9)	1.5 (3)

Issues

- Is B-anti-CD20 the current standard?
  - Yes, but consider B dose reduction in high risk pts
- Should O replace R with B?
  - Not yet
  - Greater toxicity
  - OS not impacted
- Should maintenance be used after B-CD20?
  - Not supported by current data
- Will there be a future for B in the era of targeted agents ?